PATENT COOPERATION TREATY

27 AVR. 2004

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Orlhac, Thierry
ROBIC
55, rue St-Jacques
Montréal, Québec H2Y 3X2
CANADA

IACT 16/5

Hildgen

PCT

INVITATION TO RESTRICT OR TO PAY ADDITIONAL FEES

(PCT Rule 66)

Date of mailing *(day/month/year)*	26.04.2004
Applicant's or agent's file reference 000711-0025	**REPLY OR PAYMENT DUE** within 1 month(s) from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA 03/00499	04.04.2003	05.04.2002

International Patent Classification (IPC) or both national classification and IPC
A61K9/51, A61K9/51

Applicant
UNIVERSITE DE MONTREAL et al

1. This International Examining Authority

   (i) considers that **the international application does not comply with the requirements of unity of invention** (Rule 13.1, 13.2 and 13.3) for the reasons indicated in the Annex.

   (ii) therefore considers that there are **4 inventions** claimed in the international application as indicated in the Annex.

   (iii) recalls that claims relating to inventions in respect of which no international search report has been established need not be the subject of international preliminary examination (Rule 66.1 (e)).

2. Consequently the applicant is hereby **invited**, within the time limit indicated above, **to restrict the claims** as suggested under item 3, below, **or to pay** the amount indicated below:

EUR 1530,00	x	3	=	EUR 4590,00
Fee per additional invention		number of additional inventions		total amount of additional fees

   The applicant is informed that, according to Rule 68.3 (c), **the payment of any additional fee may be made under protest**, i.e. a reasonned statement to the effect that the international application complies with the requirement of unity of invention or that the amount of the required additional fee is excessive.

3. **If the applicant opts to restrict the claims**, this Authority suggests the restriction possibilities indicated in the Annex, which in its opinion would be in compliance with the requirement of unity of invention.

4. **In the absence of any response** from the applicant, this Authority will establish the international preliminary examination report on those parts of the international application indicated in the Annex which, in the opinion of this Authority appear to relate to the main invention.

Name and mailing address of the international preliminary examining authority:

European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized Officer

von Eggelkraut-Gotta

Tel. +31 70 340-4732

INVITATION TO RESTRICT OR TO PAY ADDITIONAL FEES International application No. PCT/CA 03/00499

The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: US-A-6 139 870 (VERRECCHIA THIERRY) 31 October 2000 (2000-10-31)
D2: US-A-5 683 723 (BAZILE DIDIER ET AL) 4 November 1997 (1997-11-04)
D3: WO 01/12718 A (SEO MIN HYO ;CHOI IN JA (KR); SAMYANG CORP (KR)) 22 February 2001 (2001-02-22)
D4: NAKADA Y ET AL: "LONG-CIRCULATING NANOPARTICLES USING BIODEGRADABLE ABA TRIBLOCK COPOLYMERS CONTAINING POLY(L-LACTIC ACID) A-BLOCKS ATTACHED TO CENTRAL POLY(OXYETHYLENE) B-BLOCKS" PHARMACEUTICAL SCIENCES, LONDON, GB, vol. 3, no. 10, October 1997 (1997-10), pages 479-481, XP000783648 ISSN: 1356-6881
D5: RYU JAE-GON ET AL: "Clonazepam release from core-shell type nanoparticles of poly(epsilon-caprolactone)/poly(ethylene glycol)/poly(epsilon-caprolactone) triblock copolymers" INTERNATIONAL JOURNAL OF PHARMACEUTICS (KIDLINGTON), vol. 200, no. 2, 10 May 2000 (2000-05-10), pages 231-242, XP002257858 ISSN: 0378-5173
D6: PANOYAN AVEDIS, HILDGEN PATRICE: "Vecteurs polymériques injectables pour l'administration des anticancéreux" CONGRÈS DE L'ACFAS 2000 - COMMUNICATION PRÉSENTÉE AU CONGRES, [Online] page 1, XP002257860 Retrieved from the Internet: URL:http://www.acfas.ca/congres/congres68/ S1080.htm> [retrieved on 2003-10-14]

The IPEA agrees with the objection put forward by the ISA as to lack of unity (Rule 13.1 PCT), the reasons for the objection being as follows: the problem to be solved by the present application is a need for new stealthy polymeric biodegradable nanosphere compositions and polymers for synthesizing the same.

The solution proposed by the applicant is a stealthy biodegradable polyester-polyethylene multiblock copolymeric nanosphere.
A second solution proposed by the applicant is a polyester-polyethylene multiblock copolymer of formula (III): ABA-B'-(ABA-B')n-ABA (III).
A third solution proposed by the applicant is an improved method for preparing a polyester-polyethylene multiblock copolymer of formula (I): ABA-(c-ABA)n-c-ABA (I), wherein ABA is a PLA-PEG-PLA triblock.
A fourth solution proposed by the applicant is a method for preparing a stealthy

polymeric biodegradable nanospheres comprising a blend of polymers and a polyester;

The idea to use polyester-polyethylene multiblock copolymeric nanospheres is already known from the following prior art documents:

D1 discloses (see whole document) nanospheres comprising a PLA-PEG diblock copolymer and an anticancer agent.

D2 discloses (see whole document) stealthy biodegradable nanospheres comprising a PLA-PEG diblock copolymer.

D3 (see page 4, paragraph 4 - page 5, paragraph 1; page 5, last paragraph - page 6, paragraph 3; page 8, paragraph 2; page 10, paragraph 2, examples 10, and 11) discloses polymeric micelles of PEG-PLA-PEG or PEG-PLDO-PEG triblock copolymers and anticancer drugs.

D4 discloses (see whole document) nanospheres of PLA-POE-PLA triblock copolymer and progesterone.

D5 discloses (see page 232, right-hand column, paragraph 3 - page 233, left-hand column, paragraph 2; page 235, left-hand column, last paragraph - right-hand column, paragraph 1)nanospheres of polycaprolactone-PEG-polycaprolactone triblock copolymers and clonazepam.

D6 discloses (see whole document) nanospheres comprising PLA-PEG copolymer and an anticancer drug.

The idea to use polyester-polyethylene multiblock copolymeric nanospheres could no longer function as a special technical feature, and therefore as a single general inventive concept. In the present application, no further technical feature can be distinguished that can be regarded as a "special technical feature" involved in the technical relationship among the different inventions. Each of the inventions listed below is a distinct invention, characterized by its own technical feature, defining the contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

The common feature that gelling agents are employed can not be a special technical feature in the sense of Rule 13.2 PCT, because it is known from said prior art. Consequently the application does not relate to one invention so linked as to form a

single general inventive concept (Rule 13.1 PCT).
Consequently, there is lack of unity a posteriori.
The application relates to four distinct inventions:

1) A stealthy polymeric biodegradable nanosphere comprising a polyester-polyethylene multiblock copolymer, use thereof for the preparation of a medicament, a method for delivering a pharmaceutical compound into a mammal by administration thereof, and method for preparation thereof (claims: 1- 3 partially; 13-21 partially; 37-43 partially).

2) A polyester-polyethylene multiblock copolymer of formula (III): ABA-B'-(ABA-B')n-ABA (III), wherein A is a polyester, B is a polyethylene, B' is a dicarboxylic polyethylene and n>= 2; and a stealthy polymeric biodegradable nanosphere comprising a PLA-PEG-PLA multiblock copolymer of formula (III), use thereof for the preparation of a medicament, a method for delivering a pharmaceutical compound into a mammal by administration thereof, and method for preparation thereof (claims: 1-3 partially; 7-12; 13-21 partially; 22-28; 37-43 partially).

3) An improved method for preparing a PLA-PEG-PLA multiblock copolymer of formula (I): ABA-(c-ABA)n-c-ABA (I), wherein ABA is a PLA-PEG-PLA triblock, c is a carboxylic diacid, and n>= 2; and a stealthy polymeric biodegradable nanosphere comprising a multiblock copolymer of formula (I), use thereof for the preparation of a medicament, a method for delivering a pharmaceutical compound into a mammal by administration thereof, and method for preparation thereof (claims: 1- 3 partially; 4-6; 13-21 partially; 29-36; 37-43 partially).

4) Method for preparing a stealthy polymeric biodegradable nanospheres from an emulsion, comprising the steps of (I) preparing an organic internal phase comprising a pharmaceutical compound and a blend of polymers and a polyester; (ii) preparing an aqueous external phase; (iii) injecting both phases into a homogenization chamber having an outlet; (iv) evaporating and/or extracting the phases of step (iii); collecting the stealthy polymeric nanospheres by centrifugation or dialysis (claims: 41-43 partially; 44).

Consequently the applicant is hereby invited to restrict the claims or to pay additional fees within the time limit of one month.